DOT HS-801 288

TESTING FOR A "SOBERING PILL"

Contract No. DOT-HS-253-3-744
December 1974
Final Report

PREPARED FOR:

U.S. DEPARTMENT OF TRANSPORTATION

NATIONAL HIGHWAY TRAFFIC SAFETY ADMINISTRATION

WASHINGTON, D.C. 20590

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Technical Report Documentation Page

1. Report No.	2. Government Accession No.	3. Recipient's Catalog No.
DOT HS-801 288		

4. Title and Subtitle	5. Report Date
Testing for a "Sobering Pill"	December 1974
	6. Performing Organization Code
7. Author(s)	8. Performing Organization Report No.
Ernest P. Noble, Ph.D., M.D.	
9. Performing Organization Name and Address	10. Work Unit No. (TRAIS)
Research and Education Foundation of Orange County Medical Center 101 City Drive, So. Orange, California 92668	11. Contract or Grant No. DOT-HS-253-3-744
	13. Type of Report and Period Covered
12. Sponsoring Agency Name and Address	Final Report 4/4/72 to 8/31/74
U.S. Department of Transportation National Highway Traffic Safety Administration Office of Driver and Pedestrian Research, R&D Washington, D.C. 20590	14. Sponsoring Agency Code N43-40

15. Supplementary Notes

16. Abstract

The concept of blocking or neutralizing the effect of alcohol on the brain was investigated in a series of human tests. It was found that pharmacological agents which stimulate the dopaminergic system tend to neutralize the alcohol reduced performance impairment.

17. Key Words	18. Distribution Statement
Alcohol	This document is to the public through the National Technical Information Service, Springfield, Va. 22151

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price
Unlimited	unlimited	50	

Form DOT F 1700.7 (8-72)

Contract No.: DOT-HS-253-3-744

Complete Final Report

TESTING FOR A "SOBERING PILL"

Ernest P. Noble, Ph.D., M.D.

INTRODUCTION

Alcohol-induced intoxication, with its accompanying effects on motor coordination, judgment, attention, memory and other aspects of behavior, presents a serious threat to the health and safety of both the individual and society. There is increasing concern with minimizing the problems caused by ethanol. Recently, attention has focused on the possibility of antagonizing ethanol's effects by pharmacologically blocking or reversing its action on the central nervous system. Inquiries into the relationship between ethanol and the adrenergic system have been particularly interesting. Mendelson et al. (1) and others (2) suggested that propranolol (inderal), a β-adrenergic receptor blocking agent used in clinical medicine to control cardiac arrhythmias, may be effective as an ethanol antagonist. This claim was refuted by clinical experiments in this laboratory (3,4). Furthermore, in this study the

ethanol-propranolol interaction was shown to be significantly synergistic.

The synergistic interaction of ethanol and propranolol suggests that the depressant effects of ethanol may result, in part or in total, from blockade of β-adrenergic systems in the CNS. Therefore, drugs or agents that stimulate β-adrenergic receptors or other aspects of the adrenergic system may antagonize ethanol's action.

Therefore, we have tested the adrenergically related central stimulating agents L-dopa, Pipradrol, Aminophylline and Ephedrine for their efficacy as sobering (amethystic) agents. In addition to these adrenergic stimulants, Sted-eze, a commercially available vitamin compound purported to have sobering properties, Nikethamide, a general CNS stimulant, and Ammonium Chloride, an osmotic diuretic, were also tested for their potential as sobering agents.

METHODS

Subjects

Forty male paid volunteers between 21 and 36 years of age participated as subjects in four experiments presented in this report. All subjects were moderate drinkers, i.e., they drank several times a month or several times a week and consumed on the average 2 or more drinks on each occasion. Potential subjects underwent detailed screening which included completion of a drug and health history questionnaire, medical examination, laboratory tests (fasting blood glucose and enzyme levels) and psychiatric evaluation. Individuals with a history of cardiovascular, renal, hepatic, respiratory, metabolic or neurological dysfunction were excluded from participation. None of the subjects

were receiving prescribed medication and they were instructed to abstain from alcohol and all other drugs 24 hours prior to their experimental sessions.

During the initial screening session, the experimental procedures were explained to the subjects in detail. They were told that the interaction between alcohol and various drugs often used in the treatment of medical diseases was being studied. These drugs included L-dopa, Pipradrol, Ammonium Chloride, Vitamin B Complex, Aminophylline, Ephedrine, Nikethamide, Aminophylline-Ephedrine, or an inert substance. Any questions they had about the study were answered by the screening physician and then written consents were obtained. Ten subjects were rejected on medical criteria, five were rejected because of too light drinking histories, and twelve subjects decided not to participate in the study.

A separate qualifying training session on the Divided Attention Task was part of the screening regimen. Any subject who was unable to reach performance criterion within the standard training period was excluded from participation. Sixteen individuals were eliminated on these grounds.

Design

Eight drugs were tested during four experiments using a double-blind within-subjects design. In all sessions, each subject performed a battery of motor, physiological, cognitive, and affect measuring tasks following the administration of ethanol and either an active "pill" or a placebo "pill".

L-dopa and Sted-eze were tested employing two sessions (one drug and one placebo) per subject, whereas Aminophylline, Ephedrine, Aminophylline-Ephedrine, Pipradrol, Nikethamide, and Ammonium Chloride were tested using four sessions (three different drugs and one placebo)

per subject*. Sessions for individual subjects were spaced approximately one week apart. Order effects were minimized by careful counterbalancing of specific task variables (memory lists, divided attention tapes) in addition to counterbalancing the order of drug and placebo administration with respect to session.

Protocol

Subjects arrived for the experiment between 1:15 and 2:15 p.m. They had been instructed to eat a prescribed light breakfast before 9 a.m. and to refrain from eating or drinking anything but water after 9 a.m. Cigarette smoking was prohibited during the experiment, however subjects were allowed a maximum of two cigarettes on the day of testing. As mentioned previously, all subjects were asked to refrain from taking all drugs,prescription or otherwise, including ethanol, for 24 hours prior to the experiment. Upon arriving at the laboratory, the subjects were introduced to the experimenters and the laboratory surroundings. The experimenters had been instructed not to initiate interaction with the subject and to respond to them in as neutral a manner as possible.

The protocol followed during experimental sessions is summarized below (see Fig. 1). Testing began at approximately 1:15 p.m. Blood alcohol concentration (BAC) was measured in order to insure that the subject did not have any ethanol in his blood prior to the experimental

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* The design was changed from two sessions per subject to four sessions per subject in order to maximize the information obtained from a single subject. This was necessary because of the difficulty in recruiting subjects capable of passing our screening procedures.

session. Baseline heart rate and blood pressure were determined. The subject's height and weight were recorded and the subject was escorted to his experimental room. The ethanol dose (two drinks of equal volume as described below) was then given to and consumed by the subject over a thirty minute period. After a 15 minute ethanol absorption period, during which electrode placement was accomplished, inebriation ratings were taken and the subject ingested a "pill" containing either active drug or placebo. BAC, heart rate, and blood pressure were determined immediately after "pill" ingestion and after a 20 minute "pill"-absorption period. Testing of drugs began at 80 minutes elapsed time, twenty minutes after "pill" administration. A battery of tests were then administered including a platform-balance test of motor coordination, electroencephalographic recordings, divided attention and free recall memory assessments of attentional and cognitive performance, a mood adjective check list assessment of affect, and objective and subjective ratings of inebriation. BAC, heart rate, and blood pressure were also determined periodically. The entire session lasted 165 minutes. Timing was a critical variable in this study and was kept as constant as possible in all sessions. At the end of the experiment, subjects were fed and then driven home. Total remuneration was paid only upon completion of all experimental sessions.

Ethanol Dose

The dose of ethanol consumed in each session was equivalent to 0.8g of absolute ethanol per kilogram of body weight. This dose was designed to achieve a peak BAC of approximately 0.09 to 0.10%

(90-100mg%). Ethanol was administered in the form of equal volumes of 90 proof gin and iced mix. In the L-dopa and Sted-eze experiments, the mix was peppermint flavored lemonade; in the rest of the experiments tonic water was used.

MEASURES

Blood Alcohol Concentration

BACs, reported as per cent blood alcohol, were determined by taking breath samples with a breathanalyzer (Breathalyzer, Stephenson Corp., Model 900A). Samples were taken in duplicate during the experimental sessions. The BAC recorded represented the mean of these two values. BACs were determined at 0 minutes elapsed time (baseline), 55 minutes elapsed time (20 minutes after ethanol administration was completed), 75 minutes elapsed time (immediately before testing began), 100 minutes elapsed time (between EEG and memory) and 160 minutes elapsed time (end of experiment).

Platform-Balance Task

The platform-balance task was included in the experimental battery to give an objective measure of balance and muscle coordination. The apparatus consisted of a round platform, eighteen inches in diameter, mounted on a combination spring/pivot system. This design allowed displacement in all directions from the level balanced position. Any displacement from level was recorded by a Grass polygraph on recording chart paper. The subjects were instructed to stand on the platform, place their feet in a specified manner with respect to foot position and location, stand straight with their arms at their sides, and look

at a specified point on the wall. The subject's performance with eyes open was recorded for thirty seconds. The subjects were then instructed to close their eyes and another thirty second sample was taken. The task was performed twice during each experimental session, once 25 minutes following drug administration (sample 1) and a second time 105 minutes after drug administration (sample 2).

Analysis were performed on a twenty-second eyes-open and twenty-second eyes-closed samples. Performance on the platform was scored for 1) frequency of pen displacements greater than 2 centimeters (X's), 2) total amount of time the pen was displaced a minimum of 2 centimeters from baseline (Time), and 3) total amplitude of displacement obtained by summing the maximum displacement above 2 centimeters for each incident recorded (Peak).

Electroencephalogram

Since there is a slowing effect on the human electroencephalogram (EEG) after ethanol ingestion (5,6) it seemed important to examine the effects of possible amethystic agents on brain activity as reflected by the EEG. EEG slowing is usually associated with decreased alterness or sleep in healthy individuals. Electrodes for EEC recording were applied to the subject's scalp at frontal areas F_1 and F_2 and parietal area P_3 and were referenced to the mastoids. A five minute EEG sample was taken from each subject 30 minutes after "pill" administration in each session. EEG potentials were recorded from P_3 onto magnetic tape. Tapes were then analyzed by computer using a special program on a PDP-8 computer. One minute samples (30 second eyes-open, 30 second eyes-closed) were analyzed for each subject. The EEG spectrum was

separated into 1 or 2 Herz bands from 0-30 Hz and number of waves at each frequency band were tabulated. Activity in each band was compared across conditions and t-tests were applied.

Memory

A number of studies have shown that ethanol impairs memory and learning (7-15). In the present investigations, a free-recall memory task was selected to assess the efficacy of potential ethanol antagonists. All subjects performed the memory task during a sober training session and 55 minutes after each "pill" ingestion. A list of words was presented via tape-recorder and subjects were asked to recall as many of the words as they could in any order they wished. A different list was used in each session and none of the words appeared on more than one list. Lists were counterbalanced with session and drug. In the studies of Sted-eze and L-dopa, the word lists consisted of 30 words drawn from 5 different conceptual categories, with 6 items per category. In the studies of Pipradrol, Ammonium Chloride, Nikethamide, Aminophylline, Ephedrine and Aminophylline-Ephedrine combination, the lists contained 36 words drawn from 3 different conceptual categories, with 12 items per category. The order of item presentation was random within the constraint that no two items from the same category could appear adjacent to each other. Ninety seconds were allowed for oral recall.

Divided Attention

Among the most reliable tests which measure the deterioration of performance after the ingestion of alcohol is the divided attention (DA) task described by Moskowitz and DePry (16). This test consists of the regular presentation or absence of a tone masked by white noise

to the left ear, while a series of numbers is read in the right ear. If the subjects are instructed to only report the presence of the tone, it may be considered a signal detection task; however if the subject's task is to report the presence or absence of the tone and to repeat the numbers as heard, it was termed a divided attention test. In our study the subjects were instructed to report both the tone and the numbers.

All subjects were trained on the DA task while sober and had to achieve minimum score of 70% correct during the prescribed training period before they were accepted as subjects in the study. Subjects were required to perform the DA task 60 minutes after "pill" administration during each session. A different DA tape was used during each session. The order of tape presentation was counterbalanced with session and drug.

Mood

An important characteristic of alcohol is its ability to alter a drinker's emotional state. A close positive correlation has been found between changes in mood and BAC (1,2). In the present studies, the Green-Nowlis mood adjective check list (MACL) was used to assess the effects of various agents on subjects' reports of their affective states (see Fig. 2). Subjects completed the MACL once in each session, 90 minutes after ingestion of the"pill". The MACL is sensitive to rapid fluctuations in feelings, easily administered, reliable and provides a picture of a broad range of affects (19,20). The MACL consists of 11 factors (aggression, anxiety, surgency, elation, concentration, fatigue, social affection, sadness, skepticism,

egotism and vigor) with three adjectives per factor. Subjects checked one of 4 graded alternative responses for each adjective according to how they felt at the moment. Each adjective was assigned a score ranging from zero for "does not apply at all" to three for "applies very well". The scores for the appropriate adjectives were summed for each factor, resulting in possible factor scores of zero to nine.

Inebriation Rating

A nine item scale was developed to assess the degree of drunkenness of the subjects (see Fig. 3). The ratings, from 0 (not at all) to 100 (extremely), were made by the subjects themselves (subjective rating) as well as the experimenters (objective ratings). Subjects and experimenters completed these scales twice during each session, at the time of "pill" ingestion and 95 minutes later. Items rated on the scale were: 1) How "drunk do you feel in general? 2) How dizzy do you feel? 3) How unsteady do you feel in walking? 4) How much difficulty do you experience in controlling your muscles? 5) How difficult is it for you to speak clearly? 6) How much difficulty do you have in perceiving clearly? 7) How much difficulty do you have in thinking clearly? 8) How much are your mood and feelings affected as compared to prior to drinking the alcohol? and 9) How drunk do you feel compared to other times you have been drunk?

EXPERIMENT 1: L-dopa

L-dopa was tested using a two session design. In one session an L-dopa "pill" was given and in the other session a placebo "pill" was administered. The "pill" consisted of a powder packet, the contents

of which were stirred into 100ml of the lemonade mixture which was subsequently drunk by the subject. The L-dopa "pill" was made by transferring the contents of three 0.5g L-dopa capsules (Dopar, Eaton Labs.) into a glassine paper packet. The placebo "pill" packet contained 1.7g of a mixture of equal quantities of lactose and talc, the inert binding agents used by Eaton Labs. in their L-dopa capsules. The L-dopa packets and resultant lemonade mixture were indistinguishable from the placebo packets and lemonade mixture. The dose of 1.5g was chosen following pilot studies using a dose of 2.5g of the drug. These early studies indicated that 2.5g of L-dopa was not tolerated in a single oral dose since all four subjects given this dose became nauseous and vomited, even in the absence of ethanol. Thirteen subjects were tested with 1.5g of L-dopa. Two subjects became nauseous and vomited during the drug session. Information obtained from these two subjects was disregarded in the analysis of data.

EXPERIMENT 2: Sted-eze

Sted-eze was also tested using a two session counterbalanced design. As with L-dopa, a given subject received a Sted-eze "pill" in one session and a placebo "pill" in the other session. The "pill" was composed of 4 tablets which were swallowed with 100ml of water. The Sted-eze "pills" consisted of 4 Sted-eze tablets (Ceres Products) wrapped in aluminum foil. The placebo "pill" was 4 Sted-eze placebo tablets which were supplied by Ceres Products. The Sted-eze and placebo tablets were identical in appearance; however the active pill

had an odor, probably from the vitamin B constituents, that was lacking in the placebo tablets. Precautions were taken to avoid identification of the active tablets by the experimenters. The subjects did not seem aware of any difference in the tablets. The dose of 4 Sted-eze tablets (Vitamin B_1, 160mg; Vitamin B_2,160mg; Niacin, 45mg; yeast,1g) was chosen since this dose was purported by Ceres Products as having sobering properties. Six subjects were tested with 4 Sted-eze tablets.

EXPERIMENT 3: Ephedrine, Aminophylline, Aminophylline-Ephedrine

The three drug or drug combinations of Ephedrine, Aminophylline, and Aminophylline-Ephedrine were tested individually on the same subject; each subject participated in four experimental sessions--three drug sessions and one placebo session. During a given session, subjects received either an active "pill" or a placebo "pill". The order of drug and placebo presentation was counterbalanced across sessions. The "pill", one size 0 gelatin capsule (Lilly, No. 0), was taken with 100ml of water. Active "pills" contained either 50mg of Ephedrine sulfate U.S.P., obtained from two Lilly #114 Pulvules; 200mg of Aminophylline obtained by pulverizing, with a glass mortor and pestle, two 100mg Aminophylline tablets* (Searle #18); or 50mg of Ephedrine sulfate and 200mg Aminophylline. The placebo "pill" contained 0.35g mannitol. The four different pills were not readily distinguishable. The doses used represent the normal recommended maximum single oral dose for each agent. Eight subjects were tested with this series of drugs.

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* A small amount of mannitol had to be added to the Aminophylline in order to fill the capsule.

EXPERIMENT 4: Nikethamide, Pipradrol, Ammonium Chloride

The three drugs Nikethamide, Pipradrol, and Ammonium Chloride were tested in a manner similar to that used for Ephedrine and Aminophylline. Each subject participated in four experimental sessions, three drug and one placebo, ingesting an active "pill" or a placebo "pill" during any given session. Again, the order of drug and placebo presentation was counterbalanced. During each session in this experiment, subjects ingested a size 00 gelatin capsule (Lilly,No. 00) and 5ml of solution dispensed in a glass unit-dose container. The subject first drank the liquid and then took the capsule with 100ml of water. The active capsules contained either 2.5mg Pipradrol (Meratran, Merrel) obtained by pulverizing one 2.5mg tablet with a glass mortar and pestle, or 1.0g of Ammonium Chloride colored with yellow food coloring to match the Pipradrol capsule. The active liquid was 5ml of a 25% aqueous solution of Nikethamide (1.25g, Coramine, Ciba). The placebo capsule contained 1.0g of mannitol dyed with food coloring to match the Pipradrol* capsule. The placebo liquid consisted of quinine water. The placebo and active capsules appeared identical; however the active liquid was slightly more bitter than the placebo. The doses used represented the normal recommended maximum single oral dose for Nikethamide and Pipradrol. Eight subjects were tested with this series of drugs.

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* The total weight of the Pipradrol pill was brought up to 1.0g with mannitol.

ANALYSIS OF DATA

Tests used in this study were analyzed in the following manner. All tests of significance were performed on the difference between the placebo results and the drug results. Techniques appropraite for paired data were used. The t-test statistic was used for blood alcohol concentration, the platform-balance task, divided attention test, free recall test and EEG data. The non-parametric equivalent of the t-test for paired data, the Wilcoxon matched-pairs signed ranks test (21) was used for the mood adjective check list and for the scales of the subjective and objective ratings of inebriation. The slopes of the BAC curves for each subject were derived using the method of least squares. Slopes were calculated for the line describing the relationshop between BAC and time after ethanol ingestion. As with other data, a t-test was performed between the slopes of the ethanol-placebo condition and the ethanol-drug condition.

RESULTS*

L-dopa

In our initial studies with L-dopa, we administered a dose of 2.5g of this agent following the ingestion of ethanol. As we described in our progress report (2/14/74), this dose resulted in some drop in blood pressure; however the more problematic side effect of this dose

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* The discussion of results is organized by specific drugs. Mean scores and other relevant data are presented in tabular form by measure: BAC (Tables 1 & 2), Platform-Balance (Table 3), EEG (Table 4), Memory (Table 5), Divided Attention (Table 6), MACL (Table 7), and Inebriation Ratings (Tables 8 & 9).

of L-dopa was that it induced emesis in all of our experimental subjects. We, therefore, elected to reduce the amount of L-dopa to 1.5g and found that blood pressure remained stable and vomiting was not experienced by most subjects; however some subjects reported feelings of nausea. Despite this side effect, a number of encouraging antagonistic interactions were observed between L-dopa and ethanol. Thus, on the divided attention task, a significant improvement in tone detection ($p < 0.05$) and a nonsignificant trend toward increase in overall performance on this measure were found ($p < 0.1$) suggesting antagonism of ethanol-induced impairment of intellectual functioning. Analysis of the EEG also indicated that L-dopa tended to offset the EEG changes induced by ethanol at several frequencies (see Fig. 4). Significantly less slow activity was seen in the 3-4 Hz range ($p < 0.02$) when L-dopa was given rather than placebo. Moreover, the L-dopa group showed significantly more activity in the 9-11 Hz range ($p < 0.05$) than did the placebo group. The shift towards a greater output of fast EEG activity indicates that L-dopa may antagonize the EEG slowing induced by ethanol. L-dopa also altered ethanol-induced performance on the platform balance task*. There was a significant increase in the total amplitude of displacement with the eyes closed (Sample 1, $p < 0.05$).

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* The difference between sober and drunk performance on this task is presently under investigation, therefore, the meaning of differences in performance under drug and placebo conditions has not been established. Standardization of this task including computerization of scoring is presently underway.

Although BACs were significantly lower following L-dopa treatment than after placebo treatment ($p < 0.01$ at 20, 45, and 105 minutes after drug administration), the magnitude of the difference, approximately 0.01% at all time points, is unlikely to account for the other changes presented above. Interestingly, the slopes of the BAC curves between L-dopa and placebo conditions did not differ significantly indicating that the L-dopa-induced reduction in BAC was not due to increased ethanol elimination, but was, perhaps, due to decreased ethanol absorption.

Post-ethanol treatment with L-dopa did not affect memory performance, MACL or inebriation ratings.

It is important to note that all of the above mentioned changes occurred in spite of drug-induced malaise, including nausea, in some subjects. Reduction of the discomforting side effects of L-dopa by the concurrent administration of a peripheral decarboxylase inhibitor or augmentation of the central dopaminergic system by alternate means such as the administration of amantadine or apomorphine might prove to be more effective means of reversing ethanol's effects.

Sted-eze

Sted-eze did not antagonize ethanol's effect on any of the measures that we employed in our experimental battery. Inspite of equivalent BAC curves in the Sted-eze and placebo conditions, the EEG tended to be slowed further by the ethanol-Sted-eze combination than with the ethanol-placebo treatment. Sted-eze tended to increase

slow activity in the 1-2 Hz range ($p < 0.1$) and decrease activity in the 9-11 Hz range ($p < 0.1$). Furthermore, the number of line crosses on the platform balance task was decreased by Sted-eze treatment (Sample 1, $p < 0.1$), indicating decreased balance recovery. Sted-eze did not affect memory, divided attention, MACL, or inebriation ratings differently than placebo. In conclusion, Sted-eze does not represent a useful amethystic agent.

Ephedrine

Ephedrine (50mg) treatment significantly increased the total amplitude of displacement (eyes closed) on the platform-balance task (Sample 1, $p < 0.02$) possibly indicating increased loss of balance with this drug; however, objective inebriation rating of walking performance significantly improved ($p < 0.05$). Ephedrine altered the EEG frequency distribution. Drug treatment significantly lowered activity in the 5-6 Hz range ($p < 0.05$) and tended to lower activity in the 6-7 Hz range ($p < 0.1$). However, there was no increase in faster activity with drug treatment. The only other measure affected significantly was in the MACL. Skepticism was increased ($p < 0.01$) in the ethanol-Ephedrine versus the ethanol-placebo condition. Ephedrine did not affect BAC, platform-balance, EEG, memory, divided attention, or other inebriation ratings in a manner significantly different than placebo.

Overall, Ephedrine does not seem to represent a sufficiently powerful antagonist of ethanol's effects to be of practical importance

as an amethystic agent. This suggestion is further supported by the lack of increase in antagonism when Ephedrine was given in combination with Aminophylline.

Aminophylline

Aminophylline (200mg), the orally absorbed diethylamine salt of theophylline, significantly altered ethanol's effect on motor performance and objective rating of dizziness. This drug, given after ethanol, significantly increased the number of line crosses (eyes open) on the platform balance task (Sample 1, $p<0.05$) indicating faster recovery of balance during ethanol intoxication. In addition, there was a significant decrease in the subjects' feelings of ethanol-induced dizziness ($p<0.05$) as rated by trained observers. The EEG frequency distribution was altered by treatment with Aminophylline. When compared with placebo treatment, Aminophylline significantly increased activity in the 0-1 Hz range ($p<0.05$), significantly reduced activity in the 6-7 Hz ($p<0.05$), 7-9 Hz ($p<0.02$), 9-11 Hz ($p<0.05$), and 11-13 Hz ($p<0.05$) ranges and tended to decrease activity in the 5-6 Hz range ($p<0.1$). However, these changes do not seem to represent an Aminophylline-induced shift in activity from slow to fast or fast to slow. Interestingly, Aminophylline treatment reduced the amount of alpha activity (7-11 Hz); however there was not a concurrent 'activation' of the EEG (increase in frequencies above 11 Hz).

In contrast to the above described changes, Aminophylline

treatment did not affect BAC, memory, divided attention, other subjective and objective ratings of inebriation or the MACL. However, given some of the observed antagonistic interactions between Aminophylline and ethanol, xanthine phosphodiesterase inhibitors may represent agents capable of reversing ethanol-induced motor impairments and research on these type of compounds should be continued.

Aminophylline-Ephedrine Combination

The combination of Aminophylline (200mg) with Ephedrine (50mg), like Aminophylline alone, altered ethanol's effect on motor coordination, i.e., the drug combination increased the number of line crosses (eyes open on the platform-balance task (Sample 1, $p<0.05$). In addition, post-ethanol treatment with this drug combination tended to activate the EEG. Drug treatment significantly decreased slow activity in the 5-6 Hz range ($p< 0.01$) while significantly increasing faster activity in the 17-19 Hz range ($p<0.05$). The drug combination significantly reduced ($p<0.01$) the BAC taken 105 minutes after "pill" ingestion (Sample 5), but did not alter the slope of the BAC curve nor the BAC at other time points. The small absolute difference (0.07%) in mean BAC between conditions coupled with the lack of differences at other time points indicate that this effect does not account for other changes presented above. This drug combination did not alter ethanol's effect on memory and divided attention performance, MACL or inebriation ratings. Therefore, this drug combination does not appear to offer any significant advantages over Aminophylline given alone. Perhaps

combination of Aminophylline with a stronger ethanol-antagonist such as L-dopa may be more effective in reversing ethanol's effects

Nikethamide

Nikethamide (1.25g) antagonized some of ethanol's effects on the tests employed. Post-ethanol treatment with Nikethamide affected the platform-balance task. The number of line crosses (eyes open) decreased (Sample 2, $p < 0.02$) after Nikethamide treatment, while the time spent in the unbalanced position (eyes open) decreased (Sample 2, $p < 0.02$). Decreased line crosses have been taken to indicate decreased balance recovery. However, when coupled with a general decrease in loss of balance, as indicated by less time spent in the unbalanced position, decreased line crosses may indicate an improvement in balance. This notion is supported by a significant decrease in dizziness ($p < 0.05$) as reported by the subjects on the inebriation rating scale. The subjects also reported a decrease in ethanol-induced impairment of speech ($p < 0.05$). Nikethamide did not significantly affect other inebriation ratings. Surprisingly, this CNS stimulant did not activate the EEG. However, post-ethanol treatment with Nikethamide did significantly reduce the activity in the slow alpha 7-9 Hz range ($p < 0.02$) and tended to reduce activity in the 4-5 Hz range ($p < 0.1$). Although Nikethamide did not alter the BAC curve, the BACs taken 20 minutes after drug ingestion (Sample 3) was significantly less ($p < 0.05$) than after placebo ingestion. It is unlikely that the small magnitude of differences in mean BAC,

approximately 0.01%, could explain the other differences presented above. Nikethamide did not alter memory, divided attention, or MACL differently than placebo.

Overall, Nikethamide does not seem to represent a powerful ethanol antagonist; however, other general CNS stimulants may be more effective.

Pipradrol

Pipradrol (2.5mg), when compared with placebo, significantly reduced BACs taken 105 minutes after drug ingestion (Sample 5, $p < 0.001$); however the magnitude of decrease, approximately 0.01%, is probably not sufficient to reverse other aspects of ethanol's effects. Pipradrol also altered the EEG, decreasing activity in the 3-4 Hz range ($p < 0.05$), but did not alter ethanol's effect on platform-balance, memory, divided attention, MACL, or inebriation ratings. Therefore, Pipradrol does not seem to represent an effective sobering agent.

Ammonium Chloride

Ammonium Chloride, an osmotic diuretic, given in a single oral dose of 1.0g, did not significantly alter BAC or the BAC curve as compared to placebo. This drug decreased the number of line crosses (eyes open) on the platform-balance (Sample 2, $p < 0.05$), however total amplitude (eyes closed) tended to be reduced (Sample 2, $p < 0.1$). In contrast to this possibly synergistic effect on balancing, there was antagonism of ethanol's impairment of speech ($p < 0.05$) as

rated by the subject. In addition, Ammonium Chloride treatment tended to activate the EEG. There was a significant increase in the 21-23 Hz ($p < 0.05$) and greater than 31 Hz ranges ($p < 0.05$—note: since all activity in the EEG faster than 31 Hz was summed in this analysis bin, this result may be due to noise in the EEG recording). There were no significant interactions between ethanol and Ammonium Chloride on memory, divided attention, MACL, or inebriation ratings. At this dose, Ammonium Chloride does not appear to act as an amethystic agent.

SUMMARY AND PROSPECTUS

A number of compounds were tested for their efficacy as amethystic agents. These included L-dopa, Sted-eze, Ephedrine, Aminophylline, Aminophylline-Ephedrine Combination, Nikethamide, Pipradrol, and Ammonium Chloride. These studies on man involved the acute oral administration of ethanol (0.8 g/kg) with subsequent oral administration of each of the above drugs or a placebo using a double blind crossover design. Ethanol-drug interactions were determined via a battery of motor, physiological, cognitive, and affective measurements. The most promising amethystic agent thus far tested was L-dopa. Significant antagonistic interaction between L-dopa and ethanol was found despite some negative side effects of L-dopa at the dose that was used. These results support our earlier notions that agents which stimulate central catecholaminergic mechanisms may possess those characteristics requisite for an amethystic agent. These findings encourage future

vigorous efforts on these agents, specifically drugs that activate the dopaminergic system.

Antagonistic interactions were also found between Aminophylline (a phosphodiesterase inhibitor) and ethanol. However, at the dose used, Aminophylline did not sufficiently reverse ethanol's effects to be considered as an effective amethystic agent. On the other hand, it is entirely feasible that in combination with L-dopa or other drugs that stimulate the dopaminergic system, powerful antagonism of ethanol's effects may occur.

With respect to the other agents tested, namely Ephedrine, Aminophylline-Ephedrine combination, Nikethamide, Ammonium Chloride and Pipradrol, antagonistic interactions with ethanol on certain tests employed were observed. However, these effects were not sufficiently strong as to warrant their use as effective amethystic agents.

Finally, in all the tests used, Sted-eze failed to antagonize ethanol's effects in man; if anything, synergistic interactions between these two drugs were obtained. These results lead us to conclude that Sted-eze is not a useful amethystic agent.

The results with respect to the catecholaminergic system, specifically dopaminergic stimulation, are highly encouraging indicating that agents which activate this system have significant potential as amethystic agents; and, therefore, should receive high priority for support.

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FIGURE 1

PROTOCOL

ALCOHOL/DRUG INTERACTION STUDY

Elapsed Time	Task	Task Time
0	Breath 1	5
5	Drink 1	15
20	Drink 2	15
35	Wait (Electrode Place.)	15
50	Drug/Inebriation Rating	5
55	Breath 2	5
60	Wait (Electrode Place.)	15
75	Breath 3 (Change vial after)	5
80	Steadiness	5
85	EEG	15
100	Breath 4/Bathroom	10
110	Memory	5
115	Divided Attention	25
140	Memory	5
145	MACL	
150	Inebriation Rating	5
155	Steadiness	5
160	Breath 5/END	5

FIGURE 2

MOOD ADJECTIVE CHECK LIST

Each of the following words describes feelings of mood. Please use the list to describe your feelings at the moment you read each word. If the word definitely describes how you feel at the moment you read it, circle the double check (vv) to the right of the word. For example, if the word is relaxed and you are definitely feeling relaxed at the moment, circle the vv as follows:

relaxed (vv) v ? no. (This means you definitely feel relaxed at the moment.)

If the word only slightly applies to your feelings at the moment, circle the single check v as follows:

relaxed vv (v) ? no. (This means you feel slightly relaxed at the moment.)

If the word is not clear to you or you cannot decide whether or not it applies to your feelings at the moment, circle the question mark as follows:

relaxed vv v (?) no. (This means you cannot decide whether you are relaxed or not.)

If you definitely decide the word does not apply to your feelings at the moment, circle the no as follows:

relaxed vv v ? (no). (This means you are definitely not relaxed at the moment.)

Work rapidly. Your first reaction is best. Work down the first column, then go to the next. Please mark all words. This should take only a few minutes.

Please begin.

angry vv v ? no
clutched up vv v ? no
carefree vv v ? no
elated vv v ? no
concentrating vv v ? no
drowsy vv v ? no
affectionate vv v ? no
regretful vv v ? no
dubious vv v ? no
boastful vv v ? no
active vv v ? no
defiant vv v ? no
fearful vv v ? no
playful vv v ? no
overjoyed vv v ? no
engaged in thought vv v ? no
sluggish vv v ? no

kindly vv v ? no
sad vv v ? no
skeptical vv v ? no
egotistic vv v ? no
energetic vv v ? no
rebellious vv v ? no
jittery vv v ? no
witty vv v ? no
pleased vv v ? no
intent vv v ? no
tired vv v ? no
warmhearted vv v ? no
sorry vv v ? no
suspicious vv v ? no
self-centered vv v ? no
vigorous vv v ? no

FIGURE 3

INEBRIATION RATING

Rate your response to each question by placing a mark on the scale at the appropriate point. Each question refers to how you feel now.

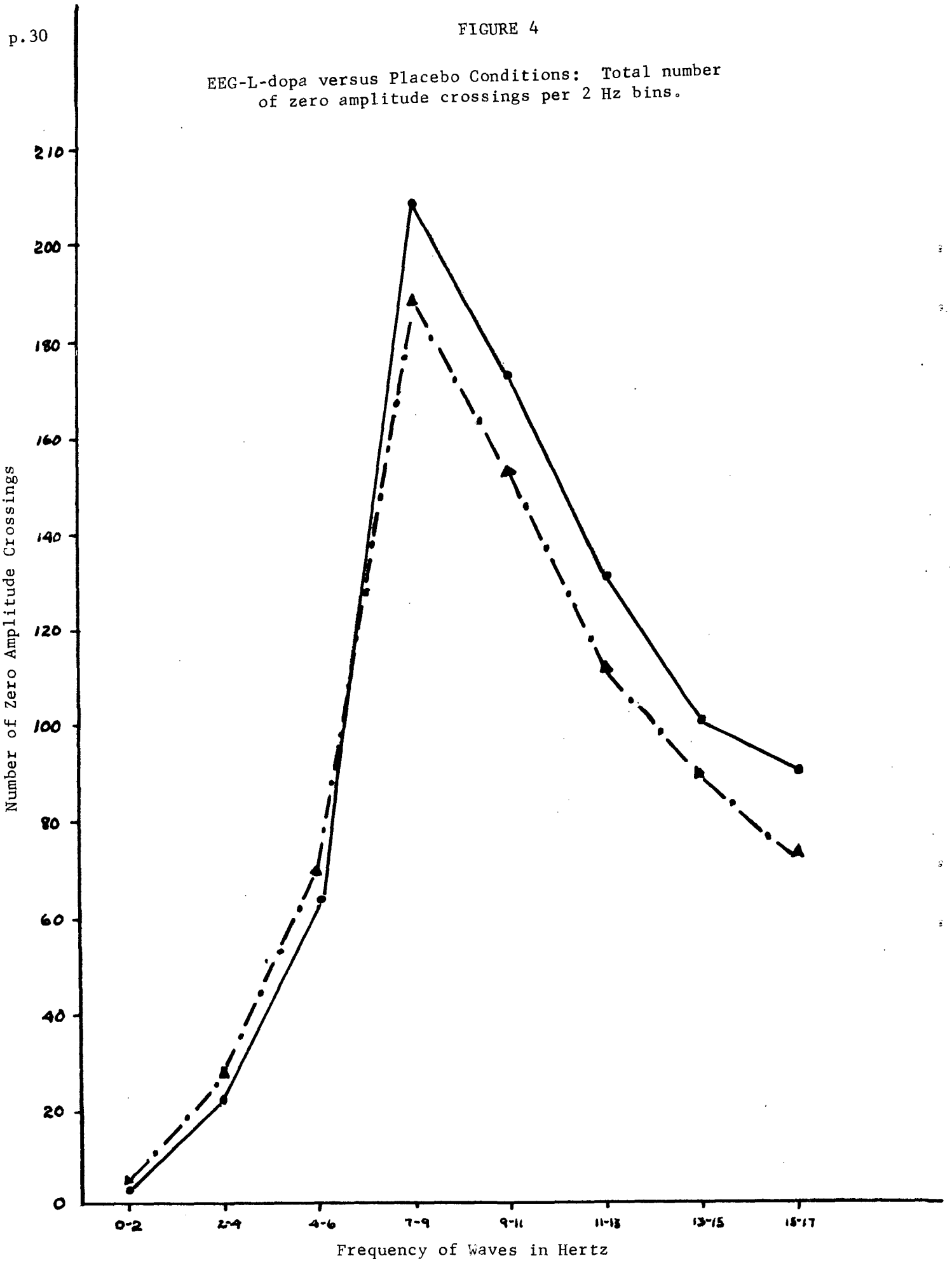
1. How "drunk" do you feel in general?	2. How dizzy do you feel?	3. How unsteady do you feel in walking?	4. How much difficulty do you experience in controlling your muscles?	5. How difficult is it for you to speak clearly?
not at all 0	not at all 0	not at all 0	not at all 0	not at all 0
10	10	10	10	10
20	20	20	20	20
a little	a little	a little	a little	a little
30	30	30	30	30
40	40	40	40	40
moderately 50	moderately 50	moderately 50	moderately 50	moderately 50
60	60	60	60	60
70	70	70	70	70
a lot	a lot	a lot	a lot	a lot
80	80	80	80	80
90	90	90	90	90
extremely 100	extremely 100	extremely 100	extremely 100	extremely 100

Figure 3-continued

• How much difficulty do you have in perceiving clearly?		7. How much difficulty do you have in thinking clearly?		8. How much are your mood and feelings affected as compared to prior to drinking the alcohol?		9. How drunk do you feel compared to other times you have been drunk?	
not at all	0	not at all	0	not at all	0	not at all	0
	10		10		10		10
	20		20		20		20
a little		a little		a little		a little	
	30		30		30		30
	40		40		40		40
moderately	50	moderately	50	moderately	50	moderately	50
	60		60		60		60
	70		70		70		70
a lot		a lot		a lot		a lot	
	80		80		80		80
	90		90		90		90
extremely	100	extremely	100	extremely	100	extremely	100

FIGURE 4

EEG-L-dopa versus Placebo Conditions: Total number of zero amplitude crossings per 2 Hz bins.



Legend for Figures

Fig. 1. Experimental Protocol: Experimental procedures were initiated at approximately 1:15 p.m. In order to facilitate intersession comparisons, experimenters strictly adhered to the time schedule outlined above. One experimental session lasted 165 minutes.

Fig. 2. Mood Adjective Check List: The MACL consisted of 11 factors (aggression, anxiety, surgency, elation, concentration, fatigue, social affection, sadness, skepticism, egotism, and vigor) with three adjectives per factor. Subjects checked one of 4 graded alternative responses for each adjective according to how they felt at the moment they were tested, 90 minutes following "pill" ingestion.

Fig. 3. Inebriation Ratings. This nice item scale designed to assess the degree of drunkenness of the subjects was completed twice during each session, at the time of "pill" ingestion and 95 minutes later. In addition to the subject's self-ratings (Inebriation Rating-Subjective), concurrent objective ratings of the subjects (Inebriation Rating-Objective) was performed by the experimenter using an identical form.

Fig. 4. Analysis of EEG samples for L-dopa and placebo conditions. Mean number of zero amplitude crossings in each 2 Hz frequency band are presented for L-dopa (-----) and placebo (—·—·—)conditions. Statistical significant differences at 3-4 Hz (p 0.02) and 9-11 Hz (p 0.05) were obtained by applying t-tests between conditions for each band (see Table 4-A).

TABLE 1

Blood Alcohol Concentration: Mean percent blood alcohol (% BAC) for drug ($\bar{X}_D$) and placebo ($\bar{X}_P$) conditions at 0 minutes (Sample 2), 20 minutes (Sample 3), 45 minutes (Sample 4), and 105 minutes (Sample 5) after "pill" ingestion.

Drug	Measure	n	% BAC $\bar{X}_D$	% BAC $\bar{X}_P$	t	p
L-dopa	Sample #2	11	0.077	0.083	1.751	NS
	3	11	0.067	0.078	3.434	<0.01
	4	11	0.066	0.076	4.481	<0.01
	5	11	0.057	0.064	3.483	<0.01
Sted-eze	Sample #2	6	0.094	0.098	0.354	NS
	3	6	0.089	0.090	0.095	NS
	4	6	0.082	0.079	-0.517	NS
	5	6	0.069	0.069	0.142	NS
Ephedrine	Sample #2	8	0.099	0.090	-1.732	NS
	3	8	0.100	0.094	-2.095	<0.1
	4	8	0.078	0.086	0.814	NS
	5	8	0.080	0.076	-0.998	NS
Aminophylline	Sample #2	8	0.093	0.090	-0.420	NS
	3	8	0.092	0.094	0.544	NS
	4	8	0.084	0.086	0.416	NS
	5	8	0.074	0.076	0.851	NS
Aminophylline-Ephedrine Combination	Sample #2	8	0.091	0.090	-0.141	NS
	3	8	0.092	0.094	0.372	NS
	4	8	0.082	0.086	1.882	NS
	5	8	0.069	0.076	3.948	<0.01
Nikethamide	Sample #2	8	0.097	0.096	-0.136	NS
	3	8	0.089	0.098	2.443	<0.05
	4	8	0.089	0.092	0.695	NS
	5	7	0.079	0.084	1.517	NS
Pipradrol	Sample #2	8	0.094	0.096	0.214	NS
	3	8	0.100	0.098	-0.450	NS
	4	8	0.091	0.091	0.080	NS
	5	7	0.071	0.082	12.669	<0.001
Ammonium Chloride	Sample #2	8	0.082	0.096	1.333	NS
	3	8	0.093	0.098	1.992	<0.1
	4	7	0.094	0.090	-1.012	NS
	5	5	0.081	0.082	0.411	NS

TABLE 2

Blood Alcohol Concentration Curve: Mean slope (% decline in 100 minutes) for drug ($\bar{X}_D$) and placebo ($\bar{X}_P$) conditions.

Drug	n	% Decline in 100 Min $\bar{X}_D$	% Decline in 100 Min $\bar{X}_P$	t	p
L-dopa	11	0.019	0.021	0.44	NS
Sted-eze	6	0.030	0.030	0.06	NS
Ephedrine	8	-0.022	-0.016	-1.18	NS
Aminophylline	8	-0.022	-0.016	-0.96	NS
Aminophylline-Ephedrine Combination	8	-0.025	-0.016	-1.62	NS
Nikethamide	8	-0.018	-0.017	0.19	NS
Pipradrol	8	-0.020	-0.017	0.26	NS
Ammonium Chloride	7	0.007	-0.021	-1.46	NS

TABLE 3-A. Platform Balance — Sample 1: Mean frequency of pen displacement greater than 2 centimeters (X's); mean total time pen displaced greater than 2 centimeters (Time); and mean total amplitude of displacement (Peak) for drug ($\bar{X}_D$) and placebo ($\bar{X}_P$) conditions.

Drug	Measure		n	$\bar{X}_D$	$\bar{X}_P$	t	p
L-dopa	Eyes Open	#X's	11	10.73	12.27	-0.69	NS
		Peak	11	52.09	59.73	-0.76	NS
		Time	11	3.95	4.51	0.60	NS
	Eyes Closed	#X's	11	17.63	17.81	-0.10	NS
		Peak	11	146.73	119.82	2.41	<0.05
		Time	11	9.07	8.15	0.81	NS
Sted-eze	Eyes Open	#X's	6	6.83	11.83	-2.09	<0.1
		Peak	6	31.50	50.00	-0.75	NS
		Time	6	2.63	2.71	-0.07	NS
	Eyes Closed	#X's	6	18.33	20.00	-0.33	NS
		Peak	6	162.66	189.00	-0.43	NS
		Time	6	9.83	11.70	-1.22	NS
Ephedrine	Eyes Open	#X's	8	18.88	14.00	-1.51	NS
		Peak	8	117.50	86.25	-0.82	NS
		Time	8	6.14	7.11	0.74	NS
	Eyes Closed	#X's	8	23.38	22.75	-0.24	NS
		Peak	8	237.75	153.25	-3.32	<0.02
		Time	8	10.25	9.60	-0.66	NS
Aminophylline	Eyes Open	#X's	8	19.88	14.00	-2.36	<0.05
		Peak	8	125.50	86.25	-1.61	NS
		Time	8	6.49	7.11	0.28	NS
	Eyes Closed	#X's	8	21.88	22.75	0.51	NS
		Peak	8	202.62	153.25	-2.23	NS
		Time	8	11.54	9.60	-1.79	NS
Aminophylline-Ephedrine Combination	Eyes Open	#X's	8	20.75	14.00	-2.64	<0.05
		Peak	8	136.00	86.25	-1.88	NS
		Time	8	7.00	7.11	0.10	NS
	Eyes Closed	#X's	8	21.75	22.75	0.27	NS
		Peak	8	227.75	153.25	-1.64	NS
		Time	8	10.16	9.60	-0.41	NS
Nikethamide	Eyes Open	#X's	8	16.38	19.00	0.96	NS
		Peak	8	95.25	130.88	1.15	NS
		Time	8	5.24	5.85	0.71	NS
	Eyes Closed	#X's	8	27.50	24.00	-1.01	NS
		Peak	8	192.62	216.38	0.72	NS
		Time	8	8.08	8.75	0.73	NS
Pipradrol	Eyes Open	#X's	8	20.38	19.00	-0.51	NS
		Peak	8	112.38	130.88	0.56	NS
		Time	8	6.29	5.85	-0.43	NS
	Eyes Closed	#X's	8	21.62	24.00	1.30	NS
		Peak	8	178.00	216.38	1.17	NS
		Time	8	8.02	8.75	0.35	NS
Ammonium Chloride	Eyes Open	#X's	8	17.38	19.00	0.42	NS
		Peak	8	104.88	118.38	0.43	NS
		Time	8	4.69	5.85	1.01	NS
	Eyes Closed	#X's	8	26.12	24.00	-0.69	NS
		Peak	8	213.62	216.38	0.10	NS
		Time	8	8.22	8.75	0.50	NS

TABLE 3-B. Platform Balance—Sample 2: Mean frequency of pen displacement greater than 2 centimeters (X's); mean total time pen displaced greater than 2 centimeters (Time); and mean total amplitude of displacement (Peak) for drug ($\bar{X}_D$) and placebo ($\bar{X}_P$) conditions.

Drug	Measure		n	$\bar{X}_D$	$\bar{X}_P$	t	p
L-dopa	Eyes Open	#X's	11	6.82	6.91	-0.05	NS
		Peak	11	29.91	32.00	-0.19	NS
		Time	11	3.39	3.14	0.26	NS
	Eyes Closed	#X's	11	20.55	18.91	0.45	NS
		Peak	11	129.10	127.82	0.06	NS
		Time	11	6.50	8.63	-1.62	NS
Sted-eze	Eyes Open	#X's	6	10.66	8.50	1.31	NS
		Peak	6	45.66	36.33	0.76	NS
		Time	6	3.13	2.81	0.43	NS
	Eyes Closed	#X's	6	20.83	19.00	0.90	NS
		Peak	6	150.83	170.16	-0.60	NS
		Time	6	9.98	10.36	-0.16	NS
Ephedrine	Eyes Open	#X's	8	18.25	13.75	-0.92	NS
		Peak	8	94.12	87.25	-0.17	NS
		Time	8	5.77	4.56	-0.67	NS
	Eyes Closed	#X's	8	25.50	24.88	-0.22	NS
		Peak	8	220.62	191.50	-0.80	NS
		Time	8	10.04	9.50	-0.25	NS
Aminophylline	Eyes Open	#X's	8	16.62	13.75	-1.24	NS
		Peak	8	107.62	87.25	-0.98	NS
		Time	8	5.19	4.56	-1.08	NS
	Eyes Closed	#X's	8	28.62	24.88	-1.48	NS
		Peak	8	196.00	191.50	-0.12	NS
		Time	8	9.39	9.50	0.08	NS
Aminophylline-Ephedrine Combination	Eyes Open	#X's	8	15.88	13.75	-0.66	NS
		Peak	8	81.00	87.25	0.30	NS
		Time	8	5.21	4.56	-0.66	NS
	Eyes Closed	#X's	8	22.62	24.88	0.67	NS
		Peak	8	158.25	191.50	0.87	NS
		Time	8	9.06	9.50	0.31	NS
Nikethamide	Eyes Open	#X's	8	13.00	20.12	3.25	<0.02
		Peak	8	81.12	107.00	1.16	NS
		Time	8	3.14	5.51	3.02	<0.02
	Eyes Closed	#X's	8	31.88	24.88	-2.10	NS
		Peak	8	292.62	249.00	-0.86	NS
		Time	8	8.55	9.26	0.50	NS
Pipradrol	Eyes Open	#X's	8	16.62	20.12	1.29	NS
		Peak	8	113.62	107.00	-0.27	NS
		Time	8	5.25	5.51	0.22	NS
	Eyes Closed	#X's	8	27.88	24.88	-0.73	NS
		Peak	8	239.58	249.00	0.25	NS
		Time	8	9.93	9.26	-0.39	NS
Ammonium Chloride	Eyes Open	#X's	8	14.12	20.12	2.97	<0.05
		Peak	8	83.75	107.00	0.94	NS
		Time	8	3.42	5.51	1.69	NS
	Eyes Closed	#X's	8	23.12	24.88	0.55	NS
		Peak	8	169.12	249.00	2.36	<0.1
		Time	8	8.74	9.26	0.22	NS

TABLE 4-A

EEG SUMMARY: L-DOPA*

Hz	$\bar{X}_D$	$\bar{X}_P$	t (n=10)	p
0-1	0.82	1.09	0.363	NS
1-2	2.09	3.36	1.161	NS
2-3	6.18	8.81	1.358	NS
3-4	14.00	19.54	2.913	<0.02
4-5	26.64	29.91	0.619	NS
5-6	36.54	39.45	0.842	NS
6-7	58.18	61.45	0.739	NS
7-9	208.27	188.45	-1.505	NS
9-11	172.36	151.64	-2.738	<0.05
11-13	130.18	111.00	-1.689	NS
13-15	100.91	88.73	-1.159	NS
15-17	89.64	72.91	-1.256	NS
17-19	78.18	62.54	-1.110	NS
19-20	26.54	22.54	-0.809	NS
20-21	57.27	47.09	-0.822	NS
21-23	58.00	53.36	-0.407	NS
23-25	63.36	52.64	-0.922	NS
25-27	38.00	27.27	-1.227	NS
27-29	38.27	28.91	-1.026	NS
29-31	41.27	32.09	-1.101	NS
31-	593.72	575.18	-0.146	NS

* Mean number of zero amplitude crossing in each frequency band (Hz) for drug ($\bar{X}_D$) and placebo ($\bar{X}_P$) conditions.

TABLE 4-B

EEG SUMMARY: STED-EZE

Hz	$\bar{X}_D$	$\bar{X}_P$	t (n=5)	p
0-1	3.20	0.40	-2.010	NS
1-2	12.60	0.60	-2.276	<0.1
2-3	15.60	4.80	-1.917	NS
3-4	21.00	10.40	-2.126	NS
4-5	25.40	23.20	-0.495	NS
5-6	20.60	33.20	1.393	NS
6-7	37.80	57.40	1.370	NS
7-9	93.80	185.20	2.051	NS
9-11	79.00	143.20	2.298	<0.1
11-13	71.00	95.60	1.091	NS
13-15	67.80	75.60	0.351	NS
15-17	73.60	69.00	-0.174	NS
17-19	72.20	68.40	-0.129	NS
19-20	25.60	21.00	-0.421	NS
20-21	52.20	46.80	-0.223	NS
21-23	60.40	48.40	-0.487	NS
23-25	67.20	49.00	-0.589	NS
25-27	30.40	27.60	-0.265	NS
27-29	34.60	28.20	-0.639	NS
29-31	41.40	32.60	-0.496	NS
31-	358.40	347.20	-0.115	NS

TABLE 4-C

EEG SUMMARY: EPHEDRINE

Hz	$\bar{X}_D$	$\bar{X}_P$	t (n=8)	P
0-1	1.00	0.37	-0.781	NS
1-2	4.37	2.62	-0.825	NS
2-3	9.12	14.62	0.904	NS
3-4	18.00	28.25	1.301	NS
4-5	32.12	37.50	1.025	NS
5-6	37.75	54.00	2.617	<0.05
6-7	50.00	71.12	1.907	<0.1
7-9	174.50	246.50	1.577	NS
9-11	152.50	204.50	1.362	NS
11-13	89.87	105.62	1.051	NS
13-15	74.25	75.37	0.075	NS
15-17	61.37	65.25	0.311	NS
17-19	49.75	49.12	-0.051	NS
19-20	15.87	17.75	0.370	NS
20-21	33.25	38.62	0.513	NS
21-23	34.87	41.62	0.636	NS
23-25	38.12	39.37	0.115	NS
25-27	17.37	22.37	0.755	NS
27-29	25.75	23.12	-0.269	NS
29-31	23.75	24.75	0.174	NS
31	378.12	259.37	-0.913	NS

TABLE 4-D

EEG SUMMARY: AMINOPHYLLINE

Hz	$\bar{X}_D$	$\bar{X}_P$	t (n=8)	p
0-1	2.87	0.37	-2.500	<0.05
1-2	5.50	2.62	-1.404	NS
2-3	14.00	14.62	0.095	NS
3-4	19.62	23.25	0.593	NS
4-5	31.75	37.50	0.826	NS
5-6	42.37	54.00	2.313	NS
6-7	54.62	71.12	2.367	<0.05
7-9	166.12	246.50	3.367	<0.02
9-11	124.12	204.50	2.923	<0.05
11-13	70.00	105.62	2.508	<0.05
13-15	60.37	75.37	0.842	NS
15-17	52.37	65.25	0.819	NS
17-19	44.00	49.12	0.400	NS
19-20	17.75	17.00	0.171	NS
20-21	36.12	38.62	0.179	NS
21-23	35.37	41.62	0.530	NS
23-25	39.25	39.37	0.009	NS
25-27	21.62	22.37	0.092	NS
27-29	27.12	23.12	-0.433	NS
29-31	28.50	24.75	-0.457	NS
31-	336.25	259.37	-0.819	NS

TABLE 4-E

EEG SUMMARY: AMINOPHYLLINE-EPHEDRINE COMBINATION

Hz	$\bar{X}_D$	$\bar{X}_P$	t (n=8)	p
0-1	0.87	0.37	-1.082	NS
1-2	7.50	2.62	-1.229	NS
2-3	11.87	14.62	0.400	NS
3-4	22.62	23.29	0.130	NS
4-5	38.87	37.50	-0.278	NS
5-6	38.87	54.00	3.599	<0.01
6-7	56.00	71.12	1.258	NS
7-9	219.75	246.50	0.994	NS
9-11	183.87	204.50	1.522	NS
11-13	111.12	105.62	-0.723	NS
13-15	85.37	75.37	-1.036	NS
15-17	71.75	65.25	-0.879	NS
17-19	70.37	49.12	-2.750	<0.05
19-20	21.75	17.75	-0.855	NS
20-21	41.75	38.62	-0.316	NS
21-23	42.37	41.62	-0.112	NS
23-25	47.50	39.37	-1.091	NS
25-27	25.75	22.37	-0.546	NS
27-29	28.00	23.12	-1.490	NS
29-31	33.12	24.75	-1.192	NS
31-	349.87	259.37	-0.958	NS

TABLE 4-F

EEG SUMMARY: NIKETHAMIDE

Hz	$\bar{X}_D$	$\bar{X}_P$	t (n=8)	p
0-1	0.62	0.38	-0.447	NS
1-2	1.62	1.88	0.179	NS
2-3	4.12	6.38	0.711	NS
3-4	9.33	14.62	1.471	NS
4-5	18.00	27.12	1.967	<0.1
5-6	23.88	33.12	1.310	NS
6-7	35.12	42.12	1.341	NS
7-9	85.29	144.50	3.176	<0.02
9-11	99.88	130.12	0.788	NS
11-13	80.00	92.75	0.522	NS
13-15	62.50	60.25	-0.141	NS
15-17	52.88	50.62	-0.188	NS
17-19	46.62	41.88	-0.056	NS
19-20	21.50	14.62	-0.813	NS
20-21	32.12	29.00	-0.472	NS
21-23	29.88	29.70	-0.023	NS
23-25	36.25	28.62	-1.123	NS
25-27	20.50	15.75	0.857	NS
27-29	23.12	16.38	-1.177	NS
29-31	21.25	17.88	-0.391	NS
31-	277.25	176.00	-1.860	NS

TABLE 4-G

EEG SUMMARY: PIPRADROL

Hz	$\bar{X}_D$	$\bar{X}_P$	t (n=8)	p
0-1	0.25	0.38	0.424	NS
1-2	2.00	1.88	-0.158	NS
2-3	7.50	6.38	-0.766	NS
3-4	9.62	14.62	2.646	<0.05
4-5	18.50	27.12	1.738	NS
5-6	29.12	33.12	0.524	NS
6-7	39.25	42.12	0.293	NS
7-9	103.75	144.50	1.737	NS
9-11	115.88	130.13	0.628	NS
11-13	86.75	92.75	0.432	NS
13-15	74.13	60.25	-1.128	NS
15-17	65.13	50.63	-1.428	NS
17-19	50.50	41.88	-0.909	NS
19-20	16.50	14.63	-0.320	NS
20-21	37.38	29.00	-1.029	NS
21-23	40.12	29.75	-0.942	NS
23-25	42.12	28.62	-1.245	NS
25-27	23.25	15.75	-1.242	NS
27-29	24.87	16.37	-1.098	NS
29-31	28.38	17.88	-1.108	NS
31-	270.50	176.00	-1.550	NS

TABLE 4- H

EEG SUMMARY: AMMONIUM CHLORIDE

Hz	$\bar{X}_D$	$\bar{X}_P$	t (n=8)	p
0-1	0.13	0.13	0.798	NS
1-2	1.88	1.88	0	NS
2-3	5.63	6.38	0.269	NS
3-4	10.13	14.62	1.446	NS
4-5	21.12	27.12	1.069	NS
5-6	25.00	33.13	1.233	NS
6-7	34.50	42.12	0.859	NS
7-9	124.88	144.50	0.902	NS
9-11	126.38	130.12	0.147	NS
11-13	83.88	92.75	0.734	NS
13-15	70.62	60.25	-1.320	NS
15-17	54.75	50.62	-0.668	NS
17-19	43.75	41.88	-0.623	NS
19-20	16.62	14.62	-0.528	NS
20-21	34.12	29.00	-1.210	NS
21-23	39.75	29.75	-2.430	<0.05
23-25	39.62	28.62	-1.774	NS
25-27	17.25	15.75	-0.887	NS
27-29	19.25	16.38	-1.172	NS
29-31	18.62	17.88	-0.230	NS
31-	283.25	176.00	-2.770	<0.05

TABLE 5

Memory Performance: Mean number of words recalled for drug ($\bar{X}_D$) and placebo ($\bar{X}_P$) conditions.

Drug	n	X_D	X_P	t	p
L-dopa	10	11.00	10.00	-1.07	NS
Sted-eze	6	11.17	11.17	0.00	NS
Ephedrine	8	14.63	14.63	0.00	NS
Aminophylline	8	16.25	14.63	-0.91	NS
Aminophylline-Ephedrine Combination	8	15.38	14.63	-0.58	NS
Nikethamide	8	12.75	13.00	0.22	NS
Pipradrol	8	12.75	13.00	0.27	NS
Ammonium Chloride	8	13.38	13.00	-0.27	NS

TABLE 6

Divided Attention Performance: Mean per cent correct (% Correct), tone errors, and number errors for drug ($\bar{X}_D$) and placebo ($\bar{X}_P$) conditions.

Drug	Measure	n	$\bar{X}_D$	$\bar{X}_P$	t	p
L-dopa	% Correct	11	73.36	69.73	-1.622	<0.1
	Tone Errors	11	15.73	20.09	2.128	<0.05
	Number Errors	11	14.18	13.09	0.776	NS
Sted-eze	% Correct	6	77.33	77.83	0.257	NS
	Tone Errors	6	18.00	19.83	0.990	NS
	Number Errors	6	6.67	5.67	-0.759	NS
Ephedrine	% Correct	8	61.63	64.25	0.624	NS
	Tone Errors	8	26.63	25.38	-0.314	NS
	Number Errors	8	16.38	15.00	-0.387	NS
Aminophylline	% Correct	8	67.50	64.25	-0.760	NS
	Tone Errors	8	22.00	25.38	1.269	NS
	Number Errors	8	16.25	15.00	-0.301	NS
Aminophylline-Ephedrine Combination	% Correct	8	65.25	64.25	-0.888	NS
	Tone Errors	8	24.00	25.38	0.568	NS
	Number Errors	8	15.12	15.00	-0.047	NS
Nikethamide	% Correct	8	66.75	66.75	0.00	NS
	Tone Errors	8	22.25	21.13	-0.370	NS
	Number Errors	8	13.50	16.88	0.754	NS
Pipradrol	% Correct	8	66.25	66.75	0.162	NS
	Tone Errors	8	20.25	21.13	0.249	NS
	Number Errors	8	18.12	16.88	-0.781	NS
Ammonium Chloride	% Correct	8	69.75	66.75	-0.818	NS
	Tone Errors	8	17.50	21.13	1.042	NS
	Number Errors	8	16.25	16.88	0.209	NS

TABLE 7

Mood Adjective Check List: Significance levels of MACL Factors obtained by comparing drug and placebo conditions using the Wilcoxin signed ranks matched pair test.

MACL Factor	L-dopa		Sted-eze		Ephedrine		Aminophylline		Aminophylline-Ephedrine Combination		Nikethamide		Pipradrol		Ammonium Chloride	
	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p
Aggression	11	NS	6	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Anxiety	10	NS	6	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Concentration	11	NS	6	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Egotism	11	NS	6	$<.06$	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Elation	10	NS	6	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Fatigue	11	NS	6	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Sadness	11	NS	6	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Skepticism	11	NS	6	NS	8	$<.01$	8	NS	8	NS	8	NS	8	NS	8	NS
Social Affection	11	NS	6	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Surgency	10	NS	6	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Vigor	11	NS	6	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS

TABLE 8

Inebriation Rating-Subjective: Significance levels of subjects inebriation ratings comparing drug and placebo conditions using the Wilcoxin signed ranks matched pair test.

	L-dopa		Sted-eze		Ephedrine		Aminophylline		Aminophylline-Ephedrine Combination		Nikethamide		Pipradrol		Ammonium Chloride	
Measure	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p
Drunk	11	NS	4	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Dizzy	11	NS	4	NS	8	NS	8	NS	8	NS	8	<0.05	8	NS	8	NS
Walking	10	NS	4	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Muscles	11	NS	4	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Speech	11	NS	4	NS	8	NS	8	NS	8	NS	8	<0.05	8	NS	8	0.05
Perceiving	10	NS	4	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Thinking	10	NS	4	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Mood	10	NS	4	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Other Drunk	10	NS	4	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS

TABLE 9

Inebriation Rating-Objective: Significance levels of experimenters inebriation ratings comparing drug and placebo conditions using the Wilcoxin signed ranks matched pair test.

	L-dopa		Sted-eze		Ephedrine		Aminophylline		Aminophylline-Ephedrine Combination		Nikethamide		Pipradrol		Ammonium Chloride	
Measure	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p
Drunk	11	NS	4	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Dizzy	11	NS	4	NS	8	NS	8	<0.05	8	NS	8	NS	8	NS	8	NS
Walking	11	NS	4	NS	8	<0.05	8	NS	8	NS	8	NS	8	NS	8	NS
Muscles	11	NS	4	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Speech	11	NS	4	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Perceiving	11	NS	4	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Thinking	11	NS	4	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Mood	11	NS	4	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS
Other Drunk	11	NS	4	NS	8	NS	8	NS	8	NS	8	NS	8	NS	8	NS